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Cardiac transplantation can be safely performed using selected diabetic donors

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Objective: Cardiac transplantation (OHT) using diabetic donors (DDs) is thought to adversely influence survival. We attempt to determine if adult OHT can be safely performed using selected DDs.

Methods: The United Network for Organ Sharing (UNOS) database was examined for adult OHT from 2000 to 2010.

Results: Of the 20,348 patients undergoing OHT, 496 (2.4%) were with DDs. DDs were older (39.6 vs 31.3 years; $P < .001$), more likely female (41.5% vs 28.3%; $P < .001$), and had a higher body mass index (BMI) (29.9 vs 26.4; $P < .001$). Recipients of DD hearts were older (53.4 vs 51.8; $P = .004$) and more likely to have diabetes (18.9% vs 14.9%; $P = .024$). The 2 groups were evenly matched with regard to recipient male gender (78.0% vs 76.1%; $P = .312$), ischemic time (3.3 vs 3.2 hours; $P = .191$), human leukocyte antigen mismatches (4.7 vs 4.6; $P = .483$), and requirement of extracorporeal membrane oxygenation (ECMO) as a bridge to transplant (0.8% vs 0.5%; $P = .382$). Median survival was similar (3799 vs 3798 days; $P = .172$). On multivariate analysis, DD was not associated with mortality (hazard ratio [HR], 1.155; 95% confidence interval [CI], 0.943-1.415; $P = .164$). As previously demonstrated, donor age, decreasing donor BMI, ischemic time, recipient creatinine, recipient black race, recipient diabetes, race mismatch, and mechanical ventilation or ECMO as a bridge to transplant were associated with mortality. On multivariate analysis of subgroups, neither insulin-dependent diabetes (1.173; 95% CI, 0.884-1.444; $P = .268$) nor duration of diabetes for more than 5 years (HR, 1.239; 95% CI, 0.914-1.016; $P = .167$) was associated with mortality.

Conclusions: OHT can be safely performed using selected DDs. Consensus criteria for acceptable cardiac donors can likely be revised to include selected DDs. (J Thorac Cardiovasc Surg 2013;146:442-7)

Cardiac transplantation remains the accepted treatment of choice for end-stage heart failure.[1] However, increasing wait list mortality and donor shortages obligate us to investigate means by which the number of available donors might be expanded. Numerous attempts to increase the donor pool have been made, and this has led to the use of donor hearts once thought to be unsuitable for transplantation.[2-8] Multiple donor and recipient characteristics have been shown to influence survival in cardiac transplantation.[9-13] Existing data on the use of hearts of diabetic donors, which otherwise fulfill standard criteria for donation, have been conflicting.[8,14] In this study, we attempt to determine whether adult cardiac transplantation can be safely performed using diabetic donors who otherwise fulfill standard criteria for organ donation according to the United Network for Organ Sharing (UNOS) database. We examined donor insulin dependence and duration of diabetes to determine whether these factors affected recipient survival. We hypothesized that cardiac transplantation could be safely performed using diabetic donors.

METHODS

Data Source

After approval from our local institutional review board, public-use data files were obtained from the UNOS registry. There were 20,348 primary, adult heart transplants performed in the United States from January 2000 to December 2010 in recipients aged 18 years or older as reported to UNOS. Of these, 496 (2.4%) patients received a donor heart from a diabetic donor. This cohort of patients was compared with patients receiving a heart from nondiabetic donors. The primary end point measured was risk-adjusted all-cause mortality. Secondary end points include acute rejection episodes before discharge and total hospital length of stay. The presence of donor diabetes in the UNOS database was based on medical history.

Statistical Analysis

Student t test and χ^2 test were used to examine continuous and categorical variables. Continuous variables are presented as mean ± standard deviation and categorical variables are reported as percentages of the total number of data points available for that field. Survival curves were

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Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
ECMO = extracorporeal membrane oxygenation
HR = hazard ratio
UNOS = United Network for Organ Sharing

generated by the Kaplan-Meier method and compared with the long-rank test. Cox proportional regression analysis was performed in 2 steps. First, covariates were run in a univariate analysis as predictors of mortality. Next, covariates with a P value < .20 were entered simultaneously in the Cox model. In addition, we tested 2-way interactions between donor diabetes and recipient age, recipient gender, donor age, donor gender, ischemic time, and recipient history of diabetes. Because none of these interactions was significant, they were not retained in the final model. Covariates missing greater than 15% of data in the registry were excluded from the analysis. Survival was determined using all-cause mortality.

RESULTS

Recipient Characteristics

Recipient characteristics are shown in Table 1. Recipients of hearts from diabetic donors were older (51.8 vs 53.4 years; $P = .004$), more likely to have diabetes themselves (14.9% vs 18.9%; $P = .024$), were more likely to receive hearts from opposite sex donors (27.7% vs 32.9%; $P = .011$), and more likely to require mechanical ventilation while awaiting transplantation (2.8% vs 4.8%; $P = .007$). The 2 groups were evenly matched with regard to gender, ethnicity, body mass index (BMI), ischemic time, cardiac output, pulmonary vascular resistance, race mismatch, number of total human leukocyte antigen mismatches, pretransplant serum creatinine, and requirement of extracorporeal membrane oxygenation (ECMO) as a bridge to transplantation.

Donor Characteristics

Donor characteristics are shown in Table 2. Donors with diabetes were older (31.3 vs 39.6 years; $P < .001$), less likely to be male (71.7 vs 58.5; $P < .001$), and had higher BMI (26.4 vs 29.9 kg/m^2; $P = .001$). Diabetic donors were also more likely to be evaluated with coronary angiography (20.5% vs 48.2%; $P < .001$) and less likely to be evaluated by echocardiography (97.5% vs 94.2%; $P < .001$). The 2 donor groups were evenly matched with regard to ejection fraction, creatinine clearance, requirement of inotropic support or vasodilators at procurement, requirement of antihypertensive agents at crossclamp, and medical history of myocardial infarction. Diabetic donors were more likely to be heavy smokers (>20 pack-year history) (24.5% vs 28.8%; $P = .031$), have a history of cancer (1.7% vs 3.6%; $P = .007$), or display clinical signs of infection (37.4% vs 42.9%; $P = .016$). There were 84 (16.9%) diabetic donors whose hearts were transplanted into diabetic recipients.

Posttransplant Outcomes

Posttransplant outcomes are shown in Table 3. When outcomes in recipients of selected diabetic donors were compared with outcomes in recipients who received organs from nondiabetic donors, there was no difference in number of acute rejection episodes during initial hospitalization, length of stay, and need for retransplantation.

Mortality

Kaplan-Meier survival curves comparing recipients of hearts from diabetic donors with the control group are shown in Figure 1, *A*. There was no significant difference in 1-year (84.2% vs 87.0%) and 3-year survival (73.1% vs 70.1%; $P = .172$). On univariate analysis, use of diabetic donor hearts was not associated with increased mortality (hazard ratio [HR]; 1.126, 95% confidence interval [CI], 0.949-1.336; $P = .172$). The results of Cox proportional regression analysis are shown in Table 4. On Cox proportional regression analysis, receiving a diabetic donor heart (HR, 1.155; 95% CI, 0.943-1.415; $P = .164$) was not independently associated with mortality. As previously described, variables associated with mortality included increasing donor age (HR, 1.012 per year; 95% CI, 1.010-1.015; $P < .001$), longer ischemic time (HR, 1.096 per hour; 95% CI, 1.065-1.128; $P < .001$), recipient creatinine (HR, 1.108/mg/dL; 95% CI, 1.082-1.134; $P < .001$), recipient black race (HR, 1.343; 95% CI, 1.231-1.465; $P < .001$), race mismatch (HR, 1.098; 95% CI, 1.023-1.178; $P = .010$), and use of mechanical ventilation (HR, 2.266; 95% CI, 1.954-2.628; $P < .001$), or ECMO (HR, 2.550; 95% CI, 1.854-3.506; $P < .001$) as a bridge to transplantation. Increasing donor BMI was associated with survival (HR, 0.989/kg/m^2; 95% CI, 0.983-0.995; $P = .003$). In addition, there were no significant interactions between diabetic donor hearts and recipient age ($P = .986$), recipient gender ($P = .991$), donor age ($P = .525$), donor gender ($P = .461$), ischemic time (0.302), or recipient diabetes ($P = .792$). Median follow-up for the study group was 1189.5 days.

Of the 496 diabetic donors, 222 (44.8%) had insulin-dependent diabetes. As shown in Figure 1, *B*, there was no significant difference in survival when comparing recipients of insulin-dependent diabetic donor hearts to non–insulin-dependent diabetic donor hearts nor to the control group.

Of the 496 diabetic donors, 182 (36.7%) had a history of diabetes mellitus for over 5 years. There was no difference in median survival when using donors with a history of diabetes mellitus for greater than 5 years when compared with those with diabetes mellitus for 5 years or less or with the control group (Figure 1, *C*). On Cox proportional regression analysis of these subgroups, neither insulin-dependent diabetes (HR,

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TABLE 1. Baseline recipient characteristics

	No. available	Nondiabetic donor (n = 19,852)	No. available	Diabetic donor (n = 496)	*P* value
Age (y)	19,852	51.8 ± 12.4	496	53.4 ± 11.8	.004
Male gender	19,852	15,100 (76.1)	496	387 (78.0)	.312
White	19,852	14,459 (72.8)	496	366 (73.8)	.697
Black	19,852	3,286 (16.6)	496	89 (17.9)	—
Hispanic	19,852	829 (4.2)	496	16 (3.2)	—
Asian	19,852	475 (2.4)	496	8 (1.6)	—
American Indian/Alaskan	19,852	64 (0.3)	496	0 (0.0)	—
Hawaiian/Pacific Islander	19,852	51 (0.3)	496	1 (0.2)	—
Multiracial	19,852	686 (3.5)	496	16 (3.2)	—
Recipient BMI	19,176	26.9 ± 21.9	483	27.2 ± 5.1	.798
Recipient diabetes		2,633 (14.9)		84 (18.9)	.024
Mean ischemic time (h)	18,627	3.2 ± 1.0	469	3.3 ± 1.1	.191
Cardiac output (L/min)	17,773	4.3 ± 1.4	442	4.2 ± 1.3	.255
Mean PVR (Wood units)	15,304	2.37 ± 2.0	394	2.5 ± 2.4	.191
Sex mismatch	19,852	5,500 (27.7)	496	163 (32.9)	.011
Race mismatch	19,852	8,551 (43.1)	496	220 (44.4)	.569
No. of HLA mismatches	16,880	4.6 ± 1.1	430	4.7 ± 1.1	.483
Creatinine before transplant (mg/dL)	19,448	1.4 ± 0.9	486	1.4 ± 0.7	.882
Creatinine clearance (mL/min)	19,230	82.0 ± 38.6	480	80.8 ± 32.3	.438
Mechanical ventilation before transplant	19,852	553 (2.8)	496	24 (4.8)	.007
ECMO before transplant	19,852	103 (0.5)	496	4 (0.8)	.382

BMI, Body mass index; *PVR*, pulmonary vascular resistance; *HLA*, human leukocyte antigen; *ECMO*, extracorporeal membrane oxygenation.

1.173; 95% CI, 0.884-1.444; $P = .268$) nor duration of diabetes over 5 years (HR, 1.239; 95% CI, 0.914-1.016; $P = .167$) was associated with mortality after cardiac transplantation.

We wished to test the hypothesis that outcome was superior in patients who received a heart from a diabetic donor who had undergone coronary angiography. Therefore, subgroup analysis was carried out on the 238 (48.2%) of diabetic donors that were evaluated with coronary angiography. Cox proportional regression analysis of this subgroup showed no association with mortality (HR, 1.191; 95% CI, 0.891-1.591; $P = .238$). Similarly, use of diabetic donor hearts that were not evaluated with coronary angiography was not associated with mortality (HR, 1.129; 95% CI, 0.851-1.498; $P = .400$).

CONCLUSIONS

Heart transplantation remains the gold standard for end-stage heart failure.[1,15,16] Increased efforts in expanding the donor pool have led to the use of donor hearts once thought to be unsafe for transplantation.[2-8] This has

TABLE 2. Donor characteristics

	No. available	Nondiabetic donor (n = 19,852)	No. available	Diabetic donor (n = 496)	*P* value
Donor age (y)	19,852	31.3 ± 12.3	496	39.6 ± 11.5	<.001
Donor Male	19,852	14,226 (71.7)	496	290 (58.5)	<.001
Donor BMI	19,852	26.4 ± 5.5	496	29.9 ± 6.7	<.001
Donor heavy cigarette use	19,740	4,832 (24.5)	459	141 (28.8)	.031
Ejection fraction (%)	19,151	61.6 ± 7.9	480	61.7 ± 7.2	.655
Serum creatinine (mg/dL)	19,824	1.2 ± 1.1	496	1.5 ± 1.5	<.001
Creatinine clearance (mL/min)	19,824	120 ± 56.1	496	114.6 ± 61.2	.053
Evaluation with echocardiogram	19,138	18,664 (97.5)	481	453 (94.2)	<.001
Evaluation with coronary angiography	19,658	4,028 (20.5)	494	238 (48.2)	<.001
Requirement of inotropic support at procurement	14,062	7,967 (56.7)	392	237 (60.5)	.134
Requirement of antihypertensives before crossclamp	19,783	3,901 (19.7)	494	94 (19.0)	.703
Requirement of vasodilator before crossclamp	19,788	2,522 (12.8)	496	67 (13.5)	.615
History of myocardial infarction	19,784	197 (1.0)	491	8 (1.6)	.166
Donor history of cancer	19,844	338 (1.7)	495	18 (3.6)	.007
Donor cocaine use	19,492	2,572 (13.0)	491	71 (14.3)	.309
Donor history of infection	18,877	7,051 (37.4)	478	205 (42.9)	.016

BMI, Body mass index.

TABLE 3. Postoperative outcomes

	No. available	Nondiabetic donor (n = 19,852)	No. available	Diabetic donor (n = 496)	*P* value
Acute rejection episode before discharge	12,139	1,821 (15.0)	358	52 (14.5)	.863
Deaths	19,850	5,212 (26.3)	496	130 (26.2)	.926
Retransplant	19,850	216 (1.1)	496	5 (1.0)	.926
Length of stay (d)	19,620	20.1 ± 25.0	488	21.2 ± 21.9	.339

resulted in use of older donors[17-19] and organs with longer ischemic time.[20,21] In this study, we attempt to determine whether carefully selected hearts from donors with diabetes could be used with acceptable outcomes. We hypothesized that the use of carefully accepted donor hearts from persons with diabetes is safe, even in donors who are dependent on insulin or have had diabetes for more than 5 years.

Existing studies on the associations between donor diabetes and outcomes after heart transplantation are conflicting.[8,14] Smits and associates[14] designed and validated a donor scoring system for heart transplantation using the Eurotransplant Registry. In this study, donor diabetes was not associated with increased recipient mortality. However, this study consisted of only 41 diabetic donors, which did not allow for meaningful subgroup analysis. Stehlik and colleagues[8] analyzed the Cardiac Transplant Research Database, also finding no overall relationship between donor diabetes and outcomes. The authors did, however, note that in a subgroup of male donors (n = 85), worse outcomes were associated with diabetes. We were unable to demonstrate this interaction between donor gender and diabetes, as Stehlik and coworkers[8] did, nor were we able to demonstrate significant interactions between diabetic donors and donor age, recipient gender, recipient age, or ischemic time. There were 84 diabetic donor hearts that were transplanted into diabetic recipients. There was not a significant interaction between diabetic donor hearts and diabetic recipients, indicating that outcomes are no different when both donor and recipient are diabetic. As such, these findings from a large national database indicate that the use of carefully selected donor hearts that fulfill standard criteria for transplantation but also are affected by diabetes does not appear to be associated with increased recipient mortality. Given that these findings were consistent across a wide range of subgroup analyses, it is therefore likely that carefully selected hearts from donors with diabetes can be used for transplantation with acceptable outcomes.

On subgroup analysis, neither insulin dependence nor duration of diabetes was associated with increased mortality. A power analysis demonstrated that there were sufficient numbers of insulin-dependent donors. A 2-sided log-rank test with an overall sample size of 20,346 subjects (19,850 in the control group and 496 in the experimental group) achieved 91.7% power at a .05 significance level to detect a hazard ratio of 1.173 as seen in the subjects with insulin-dependent diabetes. For duration of diabetes, the same analysis achieved 99.0% power at a .05 significance level to detect a hazard ratio of 1.239 as seen in donors with duration of diabetes for over 5 years. The UNOS database does not have information regarding donor insulin requirement. Further studies are needed to determine whether degree of donor insulin dependence is associated with recipient survival. In addition, data on donor blood sugar control, severity of diabetes, or presence of end-organ damage secondary to diabetes was not available. Further research is needed to determine how these markers may affect recipient survival. This in turn may shed additional light on how to

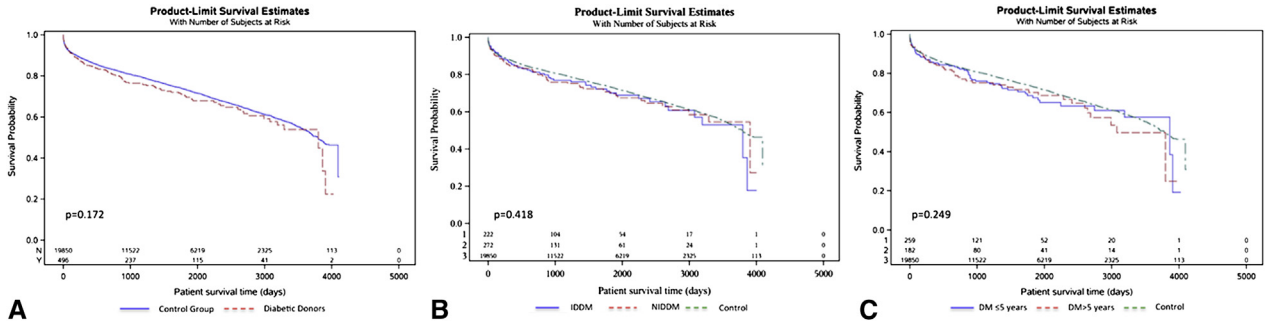

FIGURE 1. A, Kaplan-Meier survival curves comparing recipients of nondiabetic donor hearts (*N*) with patients receiving diabetic donor hearts *(Y)*. B, Comparison of recipients of insulin-dependent *(1)* and non–insulin-dependent diabetic donor hearts *(2)* with patients receiving nondiabetic donor hearts *(3)*. C, Comparison of recipients of donor hearts with a history of diabetes of 5 years or less *(1)* and more than 5 years *(2)* with patients receiving nondiabetic donor hearts *(3)*. *IDDM*, Insulin-dependent diabetes mellitus; *NIDDM*, non–insulin-dependent diabetes mellitus; *DM*, diabetes mellitus.

TABLE 4. Multiple variable model predicting risk of mortality overall

	Hazard ratio	95% Confidence interval	*P* value
Diabetic donor	1.155	0.943-1.415	.164
Donor age (per y)	1.012	1.010-1.015	<.001
Donor BMI (per kg/m^2)	0.989	0.983-0.995	.003
Donor female gender	0.943	0.875-1.017	.128
Ischemic time (per h)	1.096	1.065-1.128	<.001
Recipient creatinine (per mg/dL)	1.108	1.082-1.134	<.001
Recipient female gender	0.967	0.897-1.042	.390
Recipient age (per y)	0.999	0.996-1.002	.423
Recipient history of diabetes	1.064	0.966-1.172	.211
White race	Ref	Ref	Ref
Asian race	0.817	0.645-1.034	.093
Black race	1.343	1.231-1.465	<.001
Hispanic race	1.048	0.924-1.188	.466
Sex mismatch	1.059	0.985-1.139	.136
Race mismatch	1.098	1.023-1.178	.010
ECMO as bridge to transplant	2.550	1.854-3.506	<.001
Ventilator as bridge to transplant	2.266	1.954-2.628	<.001

BMI, Body mass index; *ECMO*, extracorporeal membrane oxygenation.

manipulate the neurohormonal brain-death milieu to maximize donor conversion. We also carried out subgroup analysis on diabetic donor hearts that were evaluated with coronary angiography. Recipients of diabetic donors that had coronary angiography did not have superior outcomes.

Recipient variables found to be associated with mortality in this study were creatinine, black race, and requirement of mechanical ventilation as a bridge to transplantation. These variables are consistent in what has been established in previous studies.[9-13,22] The requirement of ECMO as a bridge to transplantation was found to be strongly associated with death. Other factors associated with mortality in this study included race mismatch, longer ischemic time, and increasing donor age. These variables have been shown to be associated with mortality in prior studies.[9-13,23,24]

There were several limitations to this study, including those related to its retrospective nature. There are inherent limitations in using a multi-institutional database such as UNOS. Although we cannot confirm that the data are devoid of coding errors, any such errors are likely random and unlikely to create bias. In addition, UNOS does not include all potential confounders, such as detailed socioeconomic data. There are some donor characteristics that may confound the results of the study and could not be evaluated in the UNOS database, such as severity of nephropathy and presence of myocardial infarctions. Future studies are needed to determine whether these variables affect outcomes when using diabetic donors. Finally, median follow-up for this study was 1189.5 days and the use of diabetic donors may have long-term effects that could not be observed in this study period.

In conclusion, this study demonstrates that cardiac transplantation can be safely performed using carefully selected diabetic donors. Such donors can be used for transplantation with equivalent outcomes, even when the donor is insulin dependent or has had diabetes for more than 5 years.

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